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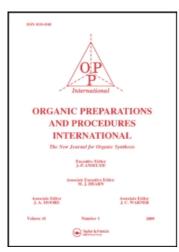
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Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t902189982

A MODIFIED STRECKER SYNTHESIS

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To cite this Article Mai, Khuong and Patil, Ghanshyam(1985) 'A MODIFIED STRECKER SYNTHESIS', Organic Preparations and Procedures International, 17: 3, 183 — 186

To link to this Article: DOI: 10.1080/00304948509355496 URL: http://dx.doi.org/10.1080/00304948509355496

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A MODIFIED STRECKER SYNTHESIS

Sumbitted by Khuong Mai* and Ghanshyam Patil (08/20/84)

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Two previous papers have shown that α -aminonitriles can be prepared in two steps from aldehydes. The α -silyloxynitriles $\underline{3}$, obtained by condensation of an aldehyde with trimethylsilyl cyanide (TMSCN), were allowed to react with various amines to afford α -aminonitriles in good

RCHO + TMSCN
$$\longrightarrow$$
 RCH-OTMS $\xrightarrow{R'R''NH}$ RCH-NR'R" $\stackrel{}{\downarrow}$ CN $\stackrel{}{\downarrow}$ CN $\stackrel{}{\downarrow}$ CN $\stackrel{}{\downarrow}$ $\stackrel{}{\downarrow}$

yields. It was also proposed that the second step of the reaction proceeds

via a Schiff base intermediate which in turn reacts with hydrogen cyanide

in an equilibrium process to produce the α-aminonitrile.

RCH-OTMS
$$\longrightarrow$$
 RCH-OH \longrightarrow RCHO $\stackrel{R'NH}{\longrightarrow}$ RCH=NR' \longrightarrow RCH-NHR' $\stackrel{|}{\longrightarrow}$ RCH-NHR' $\stackrel{|}{\longrightarrow}$ CN $\stackrel{|}{\longrightarrow}$ CN

The proposed mechanism being in accord with the observed asymmetric induction, 2,3 indicates that the silyloxynitrile 3 is not necessarily the key intermediate for this high yield reaction, but rather implies that a mixture of an aldehyde, an amine and a source hydrogen cyanide under appropriate conditions would give the desired aminonitrile as well. This led us to treat the aldehyde directly with the amine and TMSCN in methanol, instead of going through the previously reported silyloxynitrile.

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TABLE 1. a-Aminonitrile RCH(CN)NR'R"

Entry	R	R'	R"	Yield (%)	(oC)	Salt
i	NCCH2CH2	н	н	67	130-140	Oxalate
2	3,4-(MeO) ₂ C ₆ H ₃	H	н	90	180-183	нст
3	1-Naphthyl	Н	н	95	200-203	нс1
4	\(\sum_{-}\)	H	н	69	185-189	нст
5	PhCH ₂	Н	Me ₃ C	9 8	150-153	Oxalate
6	Me ₂ CH	н	Me ₃ C	99	204-206	нс1
7	4-MeSC ₆ H ₄	Н	Me ₃ C	85	80-98	HC1
8	4-MeSC ₆ H ₄	H	ը-C ₃ H ₇	96	138-140	нсі
9	2-Furyl	Н	n-Propyl	91	123-125	HC1
10	4-MeSC ₆ H ₄	н	Me ₂ CH	90	131-132	нст
11	2-Thienyl	H	<u>i</u> -Propyl	87	128-130	- HC1
12	2-H0C ₆ H ₄	Н	PhCH ₂	78	128-130	Oxalate
13	4-MeSC ₆ H ₄	(CH ₂) ₄	,	82	128-130	HC1
14	4-MeSC ₆ H ₄	(CH ₂) ₂ 0(CH ₂) ₂	95	104-106	Free Base

TAB	LE 2. ¹ Hnmr Data ^a and Elemental Analyses				
	_		Elemental Analyses		
Ent	ry ¹ Hnmr		(Found)		
	0.0 (- 00) 0.7 (00) 1.0 (. 00)		C H N		
1	2.0 (m, 2H), 2.7 (m, 2H), 4.0 (t, 1H)	Calc.	42.21 4.55 21.10		
			(42.08) (4.63) (21.23)		
2	3.9 (d, 6H), 5.9 (s, 1H), 7.3 (m, 3H)	Calc.	52.52 5.73 12.25		
			(52.75) (5.34) (12.01)		
3	6.6 (s, 1H), 7.4-8.4 (m, 7H)	Calc.	65.90 5.07 12.25		
			(66.12) (4.98) (12.65)		
4	0.9 (s, 3H), 1.2 (m, 1H), 1.4 (s, 3H),	Calc.	62.10 8.06 13.17		
•	2.5 (m, 5H), 5.2 (m, 1H), 6.0 (s, 1H).		(61.99) (7.87) (13.26)		
_					
5	1.0 (s, 9H), 2.9 (d, 2H), 4.0 (t, 1H),	Caic.	61.63 6.90 9.59		
	7.4 (s. 5H).		(61.94) (7.23) (9.23)		
6	1.2 (d, 6H), 1.6 (s, 9H), 2.5 (m, 1H),	Calc.	56.68 10.04 14.69		
	4.7 (d, 1H).		(56.87) (10.14) (14.52)		
7	1.6 (s, 9H), 2.5 (s, 3H), 6.0 (s, 1H),	Calc.	57.64 7.07 10.35		
	7.5 (m, 4H).		(57.79) (6.89) (10.11)		
8	1.0 (t, 3H), 1.8 (m, 2H), 2.6 (s, 3H),	Calc.	56.12 6.67 10.91		
	3.1 (m, 2H), 6.0 (s, 1H), 7.5 (m, 4H).		(56.15) (6.73) (11.06)		
٥		Calc	53.86 6.53 13.96		
9	1.0 (t, 3H), 1.8 (m, 2H), 3.2 (m, 2H),	Carc.	(54.01) (6.70) (13.99)		
	6.3 (s, 1H), 6.6-7.8 (m, 3H).				
10	1.5 (d, 6H), 2.5 (s, 3H), 3.6 (m, 3H),	Calc.	56.12 6.67 10.91		
	6.0 (s, 1H), 7.6 (m, 4H).		(56.38) (6.41) (11.05)		
11	1.5 (d, 6H), 3.6 (m, 1H), 6.4 (s, 1H),	Calc.	49.87 6.04 12.93		
	7.2 (m, 1H), 7.7 (m, 2H).		(49.97) (6.28) (13.15)		
12	4.1 (d, 2H), 5.4 (s, 1H), 6.7-7.6 (m,	Calc.	62.18 4.91 8.54		
	9н).		(62.00) (4.72) (8.76)		
12	2.2 (m, 4H), 2.5 (s, 3H), 3.5 (m, 4H),	Calc	58.08 6.38 10.42		
10	6.1 (s, 1H), 7.3-7.8 (m, 4H).		(57.83) (6.57) (10.75)		
14	2.5 (s, 3H), 2.6 (m, 4H), 3.8 (m, 4H),	Calc.	62.86 6.50 11.28		
	4.8 (s, 1H), 7.4 (m, 4H).		(62.93) (6.49) (11.53)		

a) & in CD30D; oxalate salts determined in DMS0-d $_{6}$

Although the yields of this modified procedure are about the same as previously reported, the advantage lies in the simplicity of a one-step operation.

It is noteworthy that the silyloxynitrile 3 does not react with amines as a neat mixture even at elevated temperature. So, the role of methanol is to decompose any source of hydrogen cyanide.

EXPERIMENTAL SECTION

General Procedure. To a cold solution (0-5°) of the aldehyde (40 mmol) and the amine (30 mmol) in 30 ml of MeOH was slowly added TMSCN (60 mmol). The resulting solution was then heated at reflux for 1 hr and evaporated in vacuo to near dryness. The residue was taken up in 50 ml of ether, dried over MgSO₄ and filtered. The filtrate was acidified with gaseous hydrogen chloride (pH 2) and the product was collected. In a case where the HC1 salt is hygroscopic, the residue was dissolved in 50 ml of EtOAc and acidified with oxalic acid.

For the preparation of primary aminonitrile, the aldehyde was added to a saturated solution of methanolic ammonia, followed by the addition of TMSCN and the mixture was heated at 45° for 2 hrs.

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